UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/068,507	07/15/1998	VINCENT G. H. EIJSINK	1380-122PCT	2387

2292 7590 05/14/2002

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
SLOBODYANSKY, ELIZABETH

ART UNIT	PAPER NUMBER
1652	25

DATE MAILED: 05/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/068,507	EIJSINK ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 4, 2002 has been entered.

The amendment filed March 4, 2002 canceling claims 44-68 and adding claims 69-108 has been entered.

Claims 69-108 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 69-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 69-108 are drawn to or depend from several genera selected from the group of first inducible promoter, an IF gene, a SakK gene, a SakR gene, the expression products of said genes and functional analogs thereof.

With regard to genera of first inducible promoter, an IF gene, a SakK gene, a SakR gene and the expression products of said genes, Applicants disclose IF gene, SakK gene, SakR gene and the promoter of the SakP gene of the sakacin P producing *Lactobacillus sake* LTH673. Therefore, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. No common structural attributes identify the members of the genus. Given this lack of description of common structural attributes or characteristics that identify members of the genus of an IF gene, a SakK gene or a SakR gene having the requisite properties, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

The claims recite "a first inducible promoter" that is induced by the expression product of the SakR gene. Applicants disclose common structural elements of the promoters of the IF gene and SakP genes (Figure 4). The specification lacks information as to whether inducers of these promoters are interchangeable, i.e., whether the IF gene promoter is inducible by the SakP gene product and vice versa. No

common identifying characteristics for an inducer of each of the two inducible genes are disclosed. Therefore, the genus of "a first inducible promoter" is at most described by some structural elements without correlation to function.

There is also no teaching in the specification as to what are the common distinguishing features shared by the members of the genus of an IF promoter inducible by the expression product of an IF gene that is a gene coding for an inducer only that would distinguish it from other promoters inducible by the expression products of their respective genes in bacteriocins' clusters. Thus, the representative number of species is one.

The specification discloses the expression product of the IF gene that activates the chain of reactions resulting in the production of sakacin P. This inducer has the amino acid sequence corresponding to residues 19-37 of SEQ ID NO:3 and unlike sakacin P does not exhibit anti-microbial activity. Thus, the representative number of species is one.

Applicants describe the expression product of an IF gene as "not a lantibiotic". Therefore, any other polypeptide including the one exhibiting anti-microbial activity and encoded by the same gene as a bacteriocin is encompassed by the claims. Structural features and other properties that could distinguish said IF expression product from the prior art are missing from the disclosure. No common structural attributes identify the members of the genus.

The prior art does not teach and does not allow to predict other members of an IF gene expression product that is not a lantibiotic and is able to induce the production of a bacteriocin. As admitted by Applicants in their Remarks filed October 16, 2000 prior to the instant invention "nothing was known about inducing compounds related to bacteriocin production" (page 17, final paragraph). However, the scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. No common structural attributes identify the members of the genus. Given this lack of description of common structural attributes or characteristics that identify members of the genus of an IF gene expression product having the requisite properties, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Furthermore, while each of "first inducible promoter", "an IF gene", "a SakK gene", "a SakR gene" represents a genus, they are further broadened by encompassing functional analogs.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and

structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, claim 77 recites a plnA gene as a functional analog of the IF gene, a plnB gene as a functional analog of the SakK gene and a plnC gene or a plnD gene as a functional analogue of SakR gene. Without addressing the fact that plnA, plnB, plnC and plnD encompass genera of molecules of which only single species of plnA, plnB, plnC and plnD from *Lactobacillus plantarum* C11 are disclosed, and considering them as adequately described species, the number of the disclosed species would be equal two. These two representative species appear to be very different. For example, it is not disclosed whether plnC gene and a plnD gene both have the same function as the SakR gene. Moreover, the same gene, plnA, encodes both an inducer and a bacteriocin in the plantaricin system. The expression

product of an IF gene, an inducer, and sakacin P, a bacteriocin, are encoded by different genes. Therefore, it appears that the plantaricin system is more similar to the nisin system than to the sakacin P system. Applicants fail to point out the features of a bacteriocin cluster that impart the ability to produce both an inducing agent and a bacteriocin wherein they are not the same.

Claim 107 is drawn to a promoter inducible by a SakR gene expression product comprising undefined number of nucleotides characterized by their location "30 to 38 nucleotides downstream from a -10 region of a bacterial gene said sequence promotes transcription of an operatively linked coding nucleic acid sequence which is activated by an expression product of a SakR gene or functional analog thereof that has been activated by an expression product of SakK gene or functional analog thereof". This claim is drawn to extremely broad genus that is not described by either structure or clear function. Claim 108 depends from claim 107 and has some structural limitation. The specification teaches only one promoter from said genus, a promoter of a SakP gene (Figure 4). The specification teaches that another promoter, of a IF gene, is structurally similar (Figure 4). While the two promoters have structural similarities, it is unknown whether IF promoter is inducible by a SakR gene product or whether the SakP gene promoter is inducible by IF directly. The specification does not disclose the correlation between the structure of the promoter and its ability to be induced by a specific peptide.

Therefore, based on the instant disclosure, taken into account that the representative number of the disclosed species equals one and considering the state of the relevant art, it is unpredictable whether a nucleotide sequence will be induced by the SakR gene expression product. Thus, a promoter inducible by the expression product of an SakR gene, IF, SakK, SakR genes, their expression products and analogs lack sufficient written description.

Claims 69-108 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a gene expression system for genus *Lactobacillus* comprising a promoter inducible by the IF gene expression product, an IF gene, a SakK gene and a SakR gene from LTH673, a kit comprising it and a method of use thereof, does not reasonably provide enablement for said expression system suitable for any host and an expression system comprising functional analogs of said elements and a kit and a method of use thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

The specification teaches the system comprising the cluster IF-K-R in sakacin P producing *Lactobacillus sake* LTH673. They teach that the chain of events leading to the induction of transcription of sakacin P starts with the induction of the IF gene promoter with IF. They further teach that it possible to use this system in a lactic bacterim for temporal and/or quantitative regulation of gene of interest (e.g., page 5-6). The expression of genes under control of the inducible promoter depends on the expression of the IF-K-R gene cluster (e.g., page 7, lines 16-31). With regard to claims 69 and 70, the specification does not teach a promoter other than the IF gene promoter that is induced by IF and from which SakK and SakR genes can be expressed. However, it is unknown whether IF-K-R genes are sufficient to induce transcription of a gene of interest and therefore, whether the system would work in a host other than LAB (sentence bridging pages 10 and 11 and page 21, lines 17-20). For the same reason vectors containing some of the genes such as IF, K or R are suitable for host cells that can complement the lacking activity. The specification teaches only one such host,

Lactobacillus. Claim 94 is enabled for a *Lactobacillus* system containing the IF gene and not for a system comprising an IF peptide and an unknown inducible promoter.

The claims encompass engineered promoters and inducing agents of unknown structure. The following rejection is made over a first inducible promoter of an unknown structure inducible by a SakR gene expression product or by a functional analogue of an IF gene expression product of an unknown structure.

The specification teaches IF gene product that induces its promoter and SakR gene product that enduces the SakP promoter. A functional analogue of a gene product can be a compound of various chemical classes and not necessarily peptides. It is impossible to make a compound without knowing its structure. Consequently, it is impossible to make a promoter that is inducible by unknown compound. The specification lacks guidance as to what are other compounds in addition to amino acid residues 19-37 of SEQ ID NO:3 that can induce the IF gene promoter. Moreover, as mentioned above, an analogue can be any molecule. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

Claim 107 is drawn to a part of any bacterial gene comprising an isolated nucleic acid comprising the undefined number of nucleotides characterized by their location "30 to 38 nucleotides downstream from a -10 region of a bacterial gene". The function of said sequence is to promote "transcription of an operatively linked coding nucleic acid sequence which is activated by an expression product of a SakR gene or

functional analog thereof that has been activated by an expression product of SakK gene or functional analog thereof". The specification teaches only one such promoter, the promoter of the SakP gene from LTH673 inducible by the peptide 19-37 of SEQ ID NO: 3. This claim is so broad as to encompass various structures induced by various structures. While a promoter of claim 108 is enabled for the peptide 19-37 of SEQ ID NO: 3 it is not enabled for inducer peptides of unknown structures. The specification does not teach what are the structural requirements for the sequence to impart the requisite function. The state of the art does not allow the predictability of function based on structure.

Therefore, one of ordinary skill would require guidance, as to a host other than *Lactobacillus* for which the instant invention is suitable. One of ordinary skill would further require guidance, such as information regarding the structural limitations on a promoter and its inducer, in order to make a first inducible promoter inducible by a SakR gene product or a functional analogue of an IF gene, SakK gene and SakR gene as well as analogues of said compounds in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite IF, SakK, SakR, plnA, plnB, plnC, etc. The metes and bounds of these terms are indefinite because it is unclear what molecules are encompassed by the terms. It further confusing that some claims refer to said genes "of a lactic acid bacterium". It is unclear whether it implies that genes not from lactic acid bacteria are encompassed.

The claims are confusing as reciting a functional analogue. The metes and bounds of this term are not defined in the specification or known in the art.

Claims 73, 74, 98 and 99 are confusing. They depend from claims 69, 94 and 95, respectively, that link SakK and SakR genes to a promoter inducible by IF whereas claims 73, 74, 98 and 99 recite these genes "operably linked to a constitutive promoter".

Response to Arguments

Applicant's arguments filed February March 4, 2002 have been fully considered but they are not persuasive.

Applicants argue with regard to functional analogs that they are represented by genes of the gene cluster in *Lactobacillus sake* Lb674 that comprises six consecutive

genes all transcribed in the same direction and by plantaricin genes (pages 17 and 18). The examiner notes that applicants rely on the post-filing reference and that the genes in *Lactobacillus sake* Lb674 are assigned different terms (Huhne et al.). This stresses the importance of a clear definition of the terms. With regard to the plantaracin genes, as discussed above, they represent genera of molecules that are not clearly defined. If they were defined as genes from *Lactobacillus plantarum* C11 than the genera of IF-K-R are not adequately described in view of high variations in structure and function of the plantaricin genes and IF-K-R genes. Further applicant argue that the claims themselves describe the function (page 19). However, this is insufficient because there is no structure: function correlation common to the members of the genus.

With regard to the written description, Applicants argue that new claim 70 and 95 do not recite 'functional analogs" and therefore should not be included I the rejection (page 23). While they do not recite "functional analogs", they recite genera of IF, K, R that are not adequately described. While claims 71, 72, 96 and 97 recite a particular sequence of IF, they still recite genera of K, R (page 23). Applicants continue to refer to the plantaricin genes to assert that "there are at least two species of each gene" (page 24). In view of high variations between these two species, they are insufficient to describe the entire genus, *supra*. Applicants assert that "function alone can suffice as description" (page 25). This is not agreed with as to describe a molecule, one needs to describe its identifying characteristics and connect them to function.

With regard to the enablement Applicants argue that "The knowledge on the art of "two-component" regulatory system, of which the present invention is an example, is fairly high, as evidenced by the citation by the Examiner of four references said to anticipate the present invention. For example, there was extensive knowledge about how the genes regulating nisin expression function at the time the invention was made" (page 28). This is not persuasive, because if the invention is a particular case of a general rule, the specifics of the invention should be clearly described. Further, the invention is specifically about the system that is not nisin's. Applicants assert that the guidance is provided in Examples. This is disagreed with because the examples do not teach any host other than *Lactobacillus* and do not provide examples of systems to which the current claims are drawn. In sum, Applicants fail to point out the features of a bacteriocin gene cluster that impart the ability to produce both an inducing agent and a bacteriocin wherein they are not the same.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

May 8, 2002